

**Evaluation and Treatment of Primary
Androgen Deficiency Syndrome in Male Patients**

Jeff Unger, MD

*Director
Chino Medical Group Diabetes and Headache Intervention Center
Chino, California*

January 16, 2008

Approximately 50 % of male patients older than age 50 have inadequate gonadal function resulting in a reduction in testicular production of testosterone. Men with hypogonadal disorders develop a variety of vague symptoms which are often denied by the patient and ignored by their physician (see table 1). Timely recognition of androgen deficiency may allow patients to experience a rapid improvement in their quality of life and reduce their cardiovascular risk. However, androgen replacement therapy may alter the course of prostate cancer, especially in those individuals who have not been adequately screened for the disorder. Therefore, clinical monitoring guidelines have been published by the American Association of Clinical Endocrinologists (AACE) which should be followed for all patients undergoing androgen replacement therapy (see table 2).

Table 1

Signs and Symptoms Suggestive of Androgen Deficiency in Men

1) Aspermia, low volume ejaculate
2) Sexual dysfunction, loss of libido
3) Breast discomfort/gynecomastia
4) Loss of body (axillary and pubic) hair
5) Small /shrinking testes (< 5 mL)*
6) Osteoporosis
7) Reduced muscle bulk and strength
8) Hot flushes; sweats
9) Decreased energy, motivation, initiative, aggressiveness, self-confidence
10) Depression, dysthymia
11) Poor concentration/memory
12) Sleep disturbance
13) Fatigue
14) Increased body fat, body mass index
15) Decreased physical or work performance
16) Reduce volume of prostate tissue+

* Adult testes are usually between 20 and 30 mL in volume & from 4.5 to 6.5 cm long by 2.8 to 3.3 cm wide.

+A nonpalpable prostate suggests low testosterone levels. A prostate that is normal for age suggests reasonably normal testosterone levels. Of note, an enlarged prostate may not substantially diminish if once-normal testosterone levels have decreased.

Table 2

Monitoring Patients on Androgen Replacement Therapy

Test and Frequency	Date Performed	Comment
H & P (Every 3 months x 12, then Annually)		
Testosterone levels		Periodic monitoring especially necessary with injections
Liver Panel		Periodic monitoring especially necessary with oral meds
PSA (Baseline, 3 mos, q 6-12 mos depending on patient age)		Annually, if unchanging
DRE (Baseline, 3 mos, q 6-12 mos depending on patient age)		Annually, if unchanging
Lipids (Annually)		
CBC (Baseline, every 3 months, and then annually)		D/C if HCT > 54 %
Bone density(After 1-2 years of therapy in men with osteoporosis or low trauma fracture)		

PSA= prostate specific antigen. DRE=Digital rectal exam. CBC=complete blood count.
H & P= History and Physical. D/C= discontinue. HCT= hematocrit. q= every.

Medical conditions which favor androgen deficiency syndrome include:

- Sellar mass
- Concurrent medications: corticosteroids, ketoconazole, opioids, and spironolactone
- Alcohol abuse
- HIV related weight loss
- Chronic kidney disease
- Chronic obstructive pulmonary disease
- Infertility
- Osteoporosis in men
- Diabetes mellitus
- Cardiovascular disease

Circulating testosterone levels are normally highest during the early morning hours. Therefore, androgen testing should preferentially be performed before 10 AM and repeated if low.

Testosterone circulates principally bound to sex hormone-binding globulin (SHBG) and is *not* biologically available. Albumin bound testosterone (free-testosterone) is the active form of the hormone. Patients who are taking anticonvulsants, those with HIV or cirrhosis, and patients older than 70 years of age tend to have higher levels of SHBG and lower levels of free (biologically active) testosterone most likely secondary to increased adipose derived serum estradiol levels. Obese patients, those who use corticosteroids and those who are hypothyroid tend to have low levels of SHBG and elevated levels of free testosterone.

Although generalized population screening for androgen deficiency is not recommended, the following high risk patients should be evaluated:

- Patients over age 45 with diabetes
- Patients with obesity
- Patients with HIV
- Patients with cardiovascular disease
- Patients on long-term corticosteroid therapy
- Patients with androgen deficiency symptomatology
- Patients suspected of having hemochromatosis, chronic kidney disease, anemia, osteoporosis, and chronic lung disease

Androgen laboratory screening should be performed before 10 AM due to the circadian nature of the hormone. Normally testosterone levels are highest prior to 10 AM and begin to decline thereafter. A testosterone level < 200 ng/dL obtained prior to 10 AM probably does not need to be repeated. Repeated test should be performed again 2-4 weeks after the initial test. However, one should not expect the level of testosterone to change by +/- 50-100 ng/dL with repeat testing. The free (bioactive) form of testosterone and sex hormone binding globulin should also be evaluated during primary testing. Some physicians utilize the “free testosterone index” as follows:

- Free testosterone index= Total testosterone/sex hormone binding globulin.
- If > 0.30 the patient has ADEQUATE testosterone levels and does not require testosterone replacement therapy.

Once the diagnosis of primary androgen deficiency syndrome has been documented, patients should consider pharmacologic intervention. Verbal informed consent should be obtained regarding the benefits and risks of therapy (see table 3). Most patients begin to experience improvement in their symptomatology and quality of life within 4-7 days of beginning androgen replacement therapy. In the vast majority of patients, the benefits of androgen replacement therapy far outweigh the risks. In particular, high risk patients (such as those who are obese with diabetes) are likely to experience a reduction in their weight, improvement in their energy levels, and lower risk of myocardial infarction with androgen replacement.

Table 3

Risks and Benefits of Androgen Replacement Therapy

<i>Potential Benefits of Testosterone Replacement Therapy</i>	<i>Potential Risks of Testosterone Replacement Therapy</i>
<ul style="list-style-type: none"> • Increase lean body mass • Decrease fat mass (may help very obese patients loose weight) • Increase muscle mass and strength • Decrease pain • Increase bone density. Decrease fractures. (Prevent osteoporosis) • Improve sexual desire and sexual function • Increase sense of well-being and energy • May motivate patients to exercise • Decrease irritability and depression • Improve sleep quality • Improve memory • Reverse anemia • Lower stroke risk* • Lower risk of heart disease* 	<ul style="list-style-type: none"> • Acne and oily skin • Growth of prostate cancer • Reduced sperm production and fertility • Breast tenderness and enlargement • Male pattern balding • Difficulty urinating • Growth of previously undetected breast cancer • Induction or worsening of sleep apnea • Headache • Formulation specific side effects: <u>Oral tabs:</u> Liver and cholesterol abnormalities <u>Injections:</u> Pain, alterations in mood or libido, high blood counts in older patients <u>Patches:</u> Skin reactions <u>Gels:</u> Potential risk of transferring drug to partner or others <u>Sublingual tabs:</u> Alterations in taste, gum irritation

*In men with hypogonadism treated with replacement doses of testosterone, total cholesterol and low density lipoprotein (LDL-C) levels may modestly decrease in conjunction with minimal changes in high density lipoprotein (HDL-C). Thus investigators have speculated that the risk of cardiovascular disease may be higher in men with hypogonadism not receiving androgen replacement therapy.

Testosterone replacement therapy is contraindicated in men with prostate cancer, breast cancer or untreated prolactinoma. Careful examination of the male breast and prostate is required initially and at follow up visits. Men with symptomatic prostatism should undergo evaluation and treatment for this problem before testosterone replacement is considered. Sleep apnea and polycythemia are relative contraindications to the use of testosterone therapy. Testosterone treatment will tend to reduce sperm counts and testicular size and should not be used in men currently seeking fertility. The different pharmacologic choices for androgen replacement are shown in table 4.

Table 4

Commonly Used Testosterone Preparations

Formulation	Brand Name	Dose	Advantage	Disadvantage	\$/month
Buccal	Striant	30 mg q 12	Sustained release of T	Gum irritation, taste issues, headache	\$280
1 % Gel	Androgel	5 g 7.5 g 10 g q d		Cover application site with clothing	\$270/5 mg
	Testim	1 or 2 tubes 5 g (50 or 100 mg applied daily)			\$270/5 mg
Oral	Android	10-50 mg/d in divided doses	Cheap	Potential liver damage and lowers HDL	\$ 150/10 mg
Patch	Androderm	2.5 mg (2/day) or 5 mg/d	Mimics normal circadian T levels	Local skin irritation may reduce adherence to therapy	\$261/5 mg

T=testosterone. HDL= high density lipoprotein.

American Association of Clinical Endocrinologists, Medical Guidelines for Clinical Practice for the Evaluation and Treatment of Hypogonadism in Adult Male Patients—2002 Update.

<http://www.aace.com/pub/pdf/guidelines/hypogonadism.pdf>

Does testosterone replacement therapy (TRT) increase risk of prostate cancer?

- 1) There appears to be a higher risk of prostate cancer in men who have low levels of testosterone to begin with.
- 2) There is little evidence to support the idea that localized prostate cancer will grow with the administration of testosterone.
- 3) Metastatic cancer of the prostate does become more aggressive with TRT.
- 4) Recommendations for following PSA while on TRT
 - a. Get baseline PSA and digital rectal exam. If normal, start TRT.
 - b. Follow PSA every 6 months.
 - c. Injections of testosterone tend to increase PSA levels twice as much as gels.
 - d. If patient does have a prior history of prostate cancer and is 4-5 years from a recurrence, the use of TRT is considered acceptable if the drug will improve the patient's quality of life.

What other risks should be considered before beginning TRT?

- 1) A blood count should be done to make certain that the patient does not have a blood condition known as polycythemia which results in thickening of the blood.
- 2) Sleep apnea may be worsened with TRT.
- 3) High doses of TRT may lower the good type of cholesterol (HDL). However, overall, the benefits of TRT on cardiovascular disease far outweigh the risks associated with treatment.
- 4) Patients may have a more difficult time urinating when using TRT if they have a prior history of benign prostatic hypertrophy (BPH).